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## (54) CERVICAL MATURING AGENT

(57) A cervical maturing agent containing a prostaglandin I derivative as the active ingredient It exerts excellent maturing effect on the cervical canal without causing any uterine contraction, which makes it useful as a cervical maturing agent.

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#### Description

Technical Field

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[0001] The present invention relates to a cervical ripening agent, and new application of prostaglandin I derivatives.

Background Art

[0002] Parturition requires both softening of the cervical canal to sufficiently expand it for extracting a fetus, and contraction of the myometrium which is the uterine smooth muscle. The cervical canal is securely closed for continuation of pregnancy up to the latter stage thereof to prevent abortion and premature delivery. On the other hand, for extraction of a fetus, softening of the cervical canal proceeds after the 36th week of pregnancy accompanied with shortening (effacement) of the cervical canal. This is a change referred to as so-called "cervical ripening". The cervical ripening is an important factor which determines the process of extracting a fetus, and smooth proceeding of the ripening is required for normal proceeding of delivery. Therefore, as a pre-stage for parturition before the start of contraction of the myometrium, sufficient ripening of the cervical canal is required for safe extraction.

[0003] At present, the number of women who give birth to children in their 20s decreases, and the number of women who give birth to children in their 30s or 40s increases. It is estimated that ten years after, the number of women who give birth to children in their 20s will further decrease, and the number of women who give birth to children in their 30s will further increase. The greatest problem in the field of obstetrics and gynecology is rigidity of the parturient canal, in its turn insufficient cervical ripening, which occurs with advances in the ages of women which give birth to children. With a low degree of cervical ripening, the cervical opening is dilated by a mechanical method, or the cervical canal is softened by administration of a cervical ripening agent.

[0004] As a medicine for accelerating cervical ripening, prostaglandin  $E_2$  (abbreviated to "PGE2" hereinafter), and dehydroepiandrosterone sulfate (abbreviated to "DHAS" hereinafter) are clinically widely used at present. However, PGE2 has the problem of possibly causing excessive contraction of the myometrium. DHAS has no adverse effect of causing excessive contraction of the myometrium, but has the problem of requiring intravenous administration for npening the cervical canal, and requiring administration for a relatively long period. On the other hand, it has been reported that beraprost sodium (abbreviated to "BPS" hereinafter) which is a prostaglandin  $I_2$  derivative having no oxytocic action exhibits a cervical ripening action in mice. However, a high dosage of 100  $\mu$ g to 200  $\mu$ g (about 2 to 4 mg per kg of weight) is required, which exceeds a general clinical dosage largely, thereby causing the problem of the possibility that an adverse effect is manifested.

[0005] An object of the present invention is to provide an excellent cervical ripening accelerator for sufficiently ripening the cervical canal without causing uterine contraction.

35 Disclosure of Invention

[0006] The present invention relates to a cervical ripening agent containing as an active ingredient a prostaglandin I derivative

Brief Description of the Drawings

[0007]

Fig. 1 shows changes in maximum tension in extension of the cervical canal, which were caused by intravaginal administration of test medicines to guinea pigs.

Fig. 2 shows changes in the slope in extension of the cervical canal, which were caused by intravaginal administration of test medicines to guinea pigs.

Best Mode for Carrying Out the Invention

[0008] Although prostaglandin I derivatives of the present invention include prostaglandin  $I_2$  derivatives, particularly metaphenylene, carbacyclin and isocarbacyclin type prostaglandin  $I_2$  derivatives, the derivatives are not limited to these derivatives. Metaphenylene prostaglandin  $I_2$  derivatives are preferably used, and 4,8-inter-m-phenylene prostaglandin I derivatives represented by the following formula (I) or pharmacologically acceptable salts thereof are more preferably used.

Printed from Mimosa 00/11/17 13 02 09 Page 2

[wherein R<sup>1</sup> represents the following:

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## (A) COOR<sup>2</sup> wherein R<sup>2</sup> is:

- 1) hydrogen or a pharmacologically acceptable cation;
- 2) normal alkyl having 1 to 12 carbon atoms, or branched alkyl having 3 to 14 carbon atoms,

#### 3) -Z-R3

wherein Z is a valence bond or normal or branched alkylene represented by  $C_tH_{2t}$  wherein t represents an integer of 1 to 6, and  $R^3$  represents cycloalkyl having 3 to 12 carbon atoms or substituted cycloalkyl having 3 to 12 carbon atoms and 1 to 3 substituents  $R^4$  which is hydrogen or alkyl having 1 to 5 carbon atoms;

4) -(CH<sub>2</sub>CH<sub>2</sub>O)<sub>n</sub>CH<sub>3</sub> wherein n is an integer of 1 to 5.

#### 5) -Z-Ar1

wherein Z is defined as the same as the above, and Ar $^1$  is phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl,  $\alpha$ -furyl,  $\alpha$ -thienyl,  $\beta$ -thienyl or substituted phenyl (wherein a substituent is at least one of chlorine, bromine, fluorine, iodine, trifluoromethyl, alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl, phenoxy p-acetoamidobenzamide, -CH=N-NH-C(=0)-NH $_2$ , -NH-C(=0)-Ph, -NH-C(=0)-CH $_3$  and -NH-C(=0)-NH $_2$ ).

#### 6) -C,H,,COOR4

wherein C.H., and R4 are defined as the same as the above.

#### 7) -C,H<sub>~</sub>N(R⁴)<sub>~</sub>

wherein  $C_1H_{21}$  and  $R^4$  are defined as the same as the above.

## 8) -CH(R5)-C(=O)-R6

wherein  $R^5$  is hydrogen or benzoyl, and  $R^5$  is phenyl, p-bromophenyl, p-chlorophenyl, p-biphenyl, p-nitrophenyl, p-benzamidophenyl, or 2-naphthyl,

## 9) -C<sub>c</sub>H<sub>3c</sub>-W-R<sup>7</sup>

wherein W is -CH=CH-, -CH=CR $^7$ - or -C., C-, and R $^7$  is hydrogen or normal or branched alkyl or aralkyl having 1 to 30 carbon atoms, and p is an integer of 1 to 5, or

## 10) -CH(CH<sub>2</sub>OR<sup>8</sup>)<sub>2</sub>

wherein R<sup>®</sup> is alkyl or acyl having 1 to 30 carbon atoms,

(B) -CH2OH;

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 $(C) - C(=O)N(R^9)_2$ 

wherein R9 is hydrogen, normal alkyl having 1 to 12 carbon atoms, branched alkyl having 3 to 12 carbon atoms, cycloalkyl having 3 to 12 carbon atoms, cycloalkylalkylene having 4 to 13 carbon atoms, phenyl, substituted phenyl (wherein the substituent is defined as the same as in (A) 5)), aralkyl having 7 to 12 carbon atoms, or -SO<sub>2</sub>R<sup>10</sup> wherein R is alkyl having 1 to 10 carbon atoms, cycloalkyl having 3 to 12 carbon atoms, phenyl, substituted phenyl (the substitutent is defined as the sane as in (A) 5)), or aralkyl having 7 to 12 carbon atoms, two R<sup>9</sup> groups may be the same or different, and when one of the R<sup>9</sup> groups is -SO<sub>2</sub>R<sup>10</sup>, the other R<sup>9</sup> is not -SO<sub>2</sub>R<sup>10</sup>, or

(D) -CH<sub>2</sub>OTHP (THP is a tetrahydropyranyl group);

A is the following:

- 1) -(CH<sub>2</sub>)<sub>m</sub>-;
- 2) -CH=CH-CH<sub>2</sub>-;
- 3) -CH--CH=CH-;
- 4) -CH2-O-CH2-;
- 5) -CH=CH-;
- 6) -O-CH2-, or
- 7)-C C-.

wherein m represents an integer of 1 to 3.

Y is hydrogen, alkyl having 1 to 4 carbon atoms, chlorine, bromine, fluorine, formyl, methoxy or nitro;

35 B is -X-C(R11)(R12)OR13

> wherein R 11 is hydrogen, alkyl having 1 to 4 carbon atoms; R 13 is hydrogen, acyl having 1 to 14 carbon atoms, aroyl having 6 to 15 carbon atoms, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, or t-butyl, X is the following.

- 1) -CH<sub>3</sub>-CH<sub>3</sub>-,
- 2) -CH=CH-, or
- 3) -C C-, and

R is the following

- 1) normal alkyl having 1 to 12 carbon atoms, or branched alkyl having 3 to 14 carbon atoms;
- 2) -Z-Ar2

wherein Z is defined as the same as the above, and  $Ar^2$  represents phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, or phenyl substituted by at least one chlorine, bromine, fluorine, iodine, trifluoromethyl, alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl or phenoxy,

3) -C.H.,OR14

Printed from Mimosa 00/11/17 13 02 10 Page 4

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wherein  $C_tH_{2t}$  is defined as the same as the above, and  $R^{14}$  represents normal alkyl having 1 to 6 carbon atoms, branched alkyl having 3 to 6 carbon atoms, phenyl, phenyl substituted by at least one chlorine, bromine, fluorine, iodine, trifluoromethyl, alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl or phenoxy, cyclopentyl, cyclohexyl, or cyclopentyl or cyclohexyl substituted by 1 to 4 normal alkyl groups having 1 to 4 carbon atoms;

4) -Z-R<sup>3</sup>

wherein Z and R<sup>3</sup> are defined as the same as the above;

5) -C<sub>t</sub>H<sub>2t</sub>-CH=C(R<sup>15</sup>)R<sup>16</sup>

wherein  $C_tH_{2t}$  is defined as the same as the above, and  $R^{15}$  and  $R^{16}$  each represent hydrogen, methyl, ethyl, propyl, or butyl; or

6) -C<sub>u</sub>H<sub>2u</sub>-C=C-R<sup>17</sup>

wherein u is an integer of 1 to 7,  $C_uH_{2u}$  represents normal or branched alkyl, and  $R^{17}$  represents normal alkyl having 1 to 6 carbon atoms (when m = 3, branched ethylene  $C_2H_4$  and methyl as  $R^{17}$  are excluded);

E is hydrogen or -OR 18

wherein  $R^{18}$  represents acyl having 1 to 12 carbon atoms, aroyl having 7 to 15 carbon atoms, or  $R^2$  (wherein  $R^2$  is defined as the same as the above); and

the formula represents the d, I or dI form]

[0009] Examples of pharmacologically acceptable salts include alkali metal salts such as sodium salts, potassium salts, and the like, alkali earth metal salts such as calcium salts, magnesium salts, and the like; amine salts such as methylamine salts, dimethylamine salts, trimethylamine salts, methylpiperidine salts, ethanolamine salts, diethanolamine salts, triethanolamine salts, lysine salts, and the like, ammonium salts, basic amine acid salts; and the like.

[0010] Although at least one prostaglandin I derivative or a salt thereof can be administered to the uterus as the cervical ripening agent of the present invention, an excipient, a stabilizer, etc., which are generally used in preparation of medicines, can also be added to the cervical ripening agent. Examples of such additives include animal oil, plant oil, paraffin, gum arabic, starch, saccharides such as lactose, sucrose, glucose, dextrin, mannitol, and the like, inorganic acid salts such as calcium carbonate, calcium sulfate, and the like; organic acid salts such as sodium citrate, sodium lactate, magnesium stearate, and the like, water-soluble polymers such as methyl cellulose, gelatin, polyethylene glycol, polyvinyl alcohol, polyvinylpyrrolidone, hydroxyethyl cellulose, hydroxypropyl cellulose, and the like, alcohols such as ethanol, glycerin, propylene glycol, sorbitol, and the like; surfactants such as sorbitan fatty acid esters, polyoxyethylene fatty acid esters, glycerin fatty acid esters, and the like

[0011] The cervical ripening agent of the present invention can be used in various forms. Examples of the forms include conventional forms such as liquids such as a vaginal epipastic, semi-solids such as an ointment, a cream, a gel, and the like, solids such as a vaginal tablet, a vaginal capsule, a pessary, a vaginal suppository, and the like. The cervical ripening agent can also be used as an injection for hypodermic injection, intravenous injection, local injection or the like. Since the prostaglandin I<sub>2</sub> derivatives of the present invention are compounds which can be orally administered, forms such as a tablet, a powder, granules, a pill, a capsule, and the like can also be used.

[0012] The cervical ripening agent of the present invention can be administered in one or divided doses of 0.0001 to 1000 mg/adult, preferably 0.001 to 500 mg/adult, depending upon the symptoms, the age, uterine conditions, the form of the agent administered, etc

[0013] The cervical ripening agent of the present invention can also be used for animals other than humans. Namely, by administering the agent to an animal other than the human, it is possible to ripen the cervical canal, and accelerate delivery of a fetus. The cervical ripening agent can thus be applied to curing and treatment in pregnancy.

55 [Examples]

[0014] In order to describe the present invention in further detail, examples are described below.

Printed from Mimosa 00/11/17 13 02 11 Page | 5

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## Example 1

Cervical ripening action:

4 to 14 samples per group.

The cervical ripening actions of compounds of formula (I) were examined by using Hartley mature guinea pigs (nine-week-old, clean animals). As test medicines, the compounds shown in Table 1 were used.

[0016] In order to compare with these compounds, the action of BPS was also tested. Experiment was carried out for

Table 1

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Table 1			
	Structural Formula		
Compound-1	но и по		
Compound-2	HOM. COOH		
Compound-3	нош		
BPS	HOW		

[0017] In the test, 100 µl of a test medicine or a base thereof was administered to the vagina at 9 o'clock and 17 o'clock, and 9 o'clock on the next day, and a guinea pig was dissected to extract the cervical canal 4 hours after the final administration. Then, the cervical canal was extended at a rate of 2 mm/min to measure tension generated in the tissue with time. As an index for cervical ripening, the maximum tension generated up to breakage of the tissue, and the

slope obtained by dividing the maximum tension by the distance of extension were examined. It is thought that decreases in these values indicate ripening of the cervical canal. A test medicine was dissolved in phosphate buffered saline, and then mixed with 3% hydroxypropyl cellulose.

[0018] Figs. 1 and 2 show changes in the maximum tension and the slope, respectively, caused by the test medicines. (\*: P < 0.05, \*\*: P < 0.01, Dunnett's method, comparison with the base administration group). BPS (10µg) showed no cervical ripening action. On the other hand, compounds 1, 2 and 3 (10µg) showed the significant cervical ripening action, as compared with the base administration group.

[0019] These results reveal that compounds 1, 2 and 3 have the excellent cervical ripening action.

Industrial Applicability

[0020] The cervical ripening agent of the present invention has an excellent softening action on the cervical canal without causing uterine contraction, and is very useful as a cervical ripening agent.

Claims

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- 1. A cervical ripening agent comprising a prostaglandin I derivative as an active ingredient.
- 2. A cervical ripening agent according to Claim 1, wherein the prostaglandin I derivative is a prostaglandin I<sub>2</sub> derivative.
- 3. A cervical ripening agent according to Claim 2, wherein the prostaglandin I<sub>2</sub> derivative is a metaphenylene, carbacyclin or isocarbacyclin type prostaglandin I<sub>2</sub> derivative.
  - 4. A cervical ripening agent according to Claim 3, comprising as an active ingredient 4,8-inter-m-phenylene prostaglandin I derivative as the metaphenylene type prostaglandin I<sub>2</sub> derivative or a pharmacologically acceptable salt thereof, which is represented by the following formula(I):

(wherein R represents the following

(A) COOR2 wherein R2 is

- 1) hydrogen or a pharmacologically acceptable cation.
- 2) normal alkyl having 1 to 12 carbon atoms, or branched alkyl having 3 to 14 carbon atoms;

3) -Z-R3

wherein Z is a valence bond or normal or branched alkylene represented by  $C_tH_{2t}$  wherein t represents an integer of 1 to 6, and  $R^3$  represents cycloalkyl having 3 to 12 carbon atoms or substituted cycloalkyl having 3 to 12 carbon atoms and 1 to 3 substituents  $R^4$  which is hydrogen or alkyl having 1 to 5 carbon atoms;

4) -(CH<sub>2</sub>CH<sub>2</sub>O)<sub>n</sub>CH<sub>3</sub> wherein n is an integer of 1 to 5.

5) -Z-Ar1

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wherein Z is defined as the same as the above, and Ar¹ is phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl,  $\alpha$ -furyl,  $\alpha$ -thienyl,  $\beta$ -thienyl or substituted phenyl (wherein a substituent is at least one of chlorine, bromine, fluorine, iodine, trifluoromethyl, alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl, phenoxy, p-acetoamidobenzamide, -CH=N-NH-C(=O)-NH<sub>2</sub>, -NH-C(=O)-Ph, -NH-C(=O)-CH<sub>3</sub> and -NH-C(=O)-NH<sub>2</sub>);

6) -C,H2,COOR4

wherein C<sub>t</sub>H<sub>2t</sub> and R<sup>4</sup> are defined as the same as the above;

7) -C,H2,N(R4)2

wherein C<sub>t</sub>H<sub>2t</sub> and R<sup>4</sup> are defined as the same as the above;

8) -CH(R<sup>5</sup>)-C(=0)-R<sup>6</sup>

wherein  $R^5$  is hydrogen or benzoyl, and  $R^6$  is phenyl, p-bromophenyl, p-chlorophenyl, p-biphenyl, p-bromophenyl, p-benzamidophenyl, or 2-naphthyl;

9) -C<sub>p</sub>H<sub>2p</sub>-W-R<sup>7</sup>

wherein W is -CH=CH-, -CH=CR $^7$ - or -C $_{\pm}$ C-, and R $^7$  is hydrogen or normal or branched alkyl or aralkyl having 1 to 30 carbon atoms, and p is an integer of 1 to 5; or

10) -CH(CH2OR8),

wherein R<sup>8</sup> is alkyl or acyl having 1 to 30 carbon atoms;

(B) -CH<sub>2</sub>OH,

 $(C) - C(=O)N(R^9)_2$ 

wherein R  $^9$  is hydrogen, normal alkyl having 1 to 12 carbon atoms, branched alkyl having 3 to 12 carbon atoms, cycloalkyl having 3 to 12 carbon atoms, cycloalkylalkylene having 4 to 13 carbon atoms, phenyl, substituted phenyl (wherein the substituent is defined as the same as in (A) 5)), aralkyl having 7 to 12 carbon atoms, or  $-SO_2R$  wherein R  $^{10}$  is alkyl having 1 to 10 carbon atoms, cycloalkyl having 3 to 12 carbon atoms, phenyl, substituted phenyl (the substitutent is defined as the same as in (A) 5)), or aralkyl having 7 to 12 carbon atoms, two R $^9$  groups may be the same or different, and when one of the R $^9$  groups is  $-SO_2R$   $^{10}$ , the other R $^9$  is not  $-SO_2R$   $^{10}$ , or

(D) -CH2OTHP (THP is a tetrahydropyranyl group).

A is the following

1) -(CH<sub>2</sub>)<sub>m</sub>-

2) -CH=CH-CH<sub>2\*</sub>.

3) -CH2-CH=CH-,

4) -CH--O-CH--

5) -CH=CH-,

6) -O-CH<sub>3-</sub>, or

7) -C C-.

wherein m represents an integer of 1 to 3.

Y is hydrogen, alkyl having 1 to 4 carbon atoms, chlorine, bromine, fluorine, formyl, methoxy or nitro;

B is -X-C(R<sup>11</sup>)(R<sup>12</sup>)OR<sup>13</sup>

wherein  $R^{11}$  is hydrogen, alkyl having 1 to 4 carbon atoms;  $R^{13}$  is hydrogen, acyl having 1 to 14 carbon atoms, aroyl having 6 to 15 carbon atoms, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, or t-butyl; X is the following:

1) -CH<sub>2</sub>-CH<sub>2</sub>-;

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- 2) -CH=CH-; or
- 3) -C<sub>=</sub>C-; and

R<sup>12</sup> is the following:

- 1) normal alkyl having 1 to 12 carbon atoms, or branched alkyl having 3 to 14 carbon atoms;
- 2) -Z-Ar<sup>2</sup>

wherein Z is defined as the same as the above, and  $Ar^2$  represents phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, or phenyl substituted by at least one chlorine, bromine, fluorine, iodine, trifluoromethyl, alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl or phenoxy;

3) -C<sub>1</sub>H<sub>21</sub>OR<sup>14</sup>

wherein  $C_1H_{2t}$  is defined as the same as the above, and  $R^{14}$  represents normal alkyl having 1 to 6 carbon atoms, branched alkyl having 3 to 6 carbon atoms, phenyl, phenyl substituted by at least one chlorine, bromine, fluorine, iodine, trifluoromethyl, alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl or phenoxy, cyclopentyl, cyclohexyl, or cyclopentyl or cyclohexyl substituted by 1 to 4 normal alkyl groups having 1 to 4 carbon atoms.

4) -Z-R<sup>3</sup>

wherein Z and R<sup>3</sup> are defined as the same as the above;

5) -C,H<sub>21</sub>-CH=C(R<sup>15</sup>)R<sup>16</sup>

wherein  $C_tH_{2t}$  is defined as the same as the above, and  $R^{15}$  and  $R^{16}$  each represent hydrogen, methyl, ethyl, propyl, or butyl, or

6) -C<sub>0</sub>H<sub>20</sub>-C C-R<sup>17</sup>

wherein u is an integer of 1 to 7,  $C_uH_{2u}$  represents normal or branched alkyl, and  $R^{17}$  represents normal alkyl having 1 to 6 carbon atoms (when m = 3, branched ethylene  $C_2H_4$  and methyl as  $R^{17}$  are excluded);

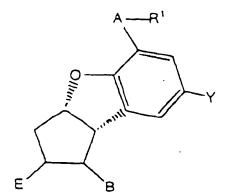
E is hydrogen or -OR18

wherein  $R^{18}$  represents acyl having 1 to 12 carbon atoms, aroyl having 7 to 15 carbon atoms, or  $R^2$  (wherein  $R^2$  is defined as the same as the above), and

the formula represents the d. I or dl form]

5. A cervical ripening agent according to Claim 4, wherein A is - (CH<sub>2</sub>)<sub>m</sub>-, -CH=CH-CH<sub>2</sub>-, -CH<sub>2</sub>-CH=CH-, -CH<sub>2</sub>-O-CH<sub>2</sub>-, -CH=CH-, -O-CH<sub>2</sub>-, or -C C- (m is 1 or 2)

- 6. A cervical ripening agent according to Claim 4, wherein A is -(CH<sub>2</sub>)<sub>2</sub>-, -CH=CH-, or -O-CH<sub>2</sub>-.
- 7. A cervical ripening method comprising administering an effective amount of prostaglandin I derivative.
- 8. A cervical ripening method according to Claim 7, wherein the prostaglandin I derivative is a prostaglandin I<sub>2</sub> derivative.
- 9. A cervical ripening method according to Claim 8, wherein the prostaglandin I<sub>2</sub> derivative is a metaphenylene, carbacyclin or isocarbacyclin type prostaglandin I<sub>2</sub> derivative.
- 10. A cervical ripening method according to Claim 9, comprising as an active ingredient 4,8-inter-m-phenylene prostaglandin I<sub>2</sub> derivative as the metaphenylene type prostaglandin I<sub>2</sub> derivative or a pharmacologically acceptable salt thereof, which is represented by the following formula(I):



Formula (I)

[wherein R + represents the following

(A) COOR2 wherein R2 is

- 1) hydrogen or a pharmacologically acceptable cation;
- 2) normal alkyl having 1 to 12 carbon atoms, or branched alkyl having 3 to 14 carbon atoms;

3) -Z-R<sup>3</sup>

wherein Z is a valence bond or normal or branched alkylene represented by  $C_tH_{2t}$  wherein t represents an integer of 1 to 6, and  $R^5$  represents cydloalkyl having 3 to 12 carbon atoms or substituted cycloalkyl having 3 to 12 carbon atoms and 1 to 3 substituents  $R^4$  which is hydrogen or alkyl having 1 to 5 carbon atoms;

4) -(CH<sub>2</sub>CH<sub>2</sub>O)<sub>n</sub>CH<sub>3</sub> wherein n is an integer of 1 to 5.

5) -Z-Ar

wherein Z is defined as the same as the above, and Ar¹ is phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl,  $\alpha$ -furyl,  $\beta$ -furyl,  $\alpha$ -thienyl,  $\beta$ -thienyl or substituted phenyl (wherein a substituent is at least one of chlorine, bromine, fluorine, iodine, trifluoromethyl, alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl, phenoxy, p-acetoamidobenzamide, -CH=N-NH-C(=O)-NH<sub>2</sub>, -NH-C(=O)-Ph, -NH-C(=O)-CH<sub>3</sub> and -NH-C(=O)-NH<sub>2</sub>).

6) -C,H $_{\sim}$ COOR $^4$  wherein C,H $_{\sim}$  and R $^4$  are defined as the same as the above,

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7) -C<sub>t</sub>H<sub>2t</sub>N(R<sup>4</sup>)<sub>2</sub>

wherein C<sub>1</sub>H<sub>21</sub> and R<sup>4</sup> are defined as the same as the above;

8) -CH(R5)-C(=O)-R6

wherein R<sup>5</sup> is hydrogen or benzoyl, and R<sup>6</sup> is phenyl, p-bromophenyl, p-chlorophenyl, p-biphenyl, p-nitrophenyl, p-benzamidophenyl, or 2-naphthyl;

9) -C<sub>p</sub>H<sub>2p</sub>-W-R<sup>7</sup>

wherein W is -CH=CH-, -CH=CR $^7$ - or -C $_{\equiv}$ C-, and R $^7$  is hydrogen or normal or branched alkyl or aralkyl having 1 to 30 carbon atoms, and p is an integer of 1 to 5; or

10) -CH(CH<sub>2</sub>OR<sup>8</sup>)<sub>2</sub>

wherein R<sup>8</sup> is alkyl or acyl having 1 to 30 carbon atoms;

(B) -CH₂OH;

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 $(C) - C(=0)N(R^9)_2$ 

wherein  $R^9$  is hydrogen, normal alkyl having 1 to 12 carbon atoms, branched alkyl having 3 to 12 carbon atoms, cycloalkylalkylene having 4 to 13 carbon atoms, phenyl, substituted phenyl (wherein the substituent is defined as the same as in (A) 5)), aralkyl having 7 to 12 carbon atoms, or  $-SO_2R$  wherein  $R^{10}$  is alkyl having 1 to 10 carbon atoms, cycloalkyl having 3 to 12 carbon atoms, phenyl, substituted phenyl (the substitutent is defined as the same as in (A) 5)), or aralkyl having 7 to 12 carbon atoms, two  $R^9$  groups may be the same or different, and when one of the  $R^9$  groups is  $-SO_2R^{10}$ , the other  $R^9$  is not  $-SO_2R^{10}$ ; or

(D) -CH2OTHP (THP is a tetrahydropyranyl group);

A is the following.

1)  $-(CH_2)_m$ -:

2) -CH=CH-CH<sub>2</sub>-;

3) -CH2-CH=CH-;

4) -CH2-O-CH2-,

5) -CH=CH-;

6) -O-CH<sub>5-</sub>, or

7) -C C-.

wherein m represents an integer of 1 to 3.

Y is hydrogen, alkyl having 1 to 4-carbon atoms, chlorine, bromine, fluorine, formyl, methoxy or nitro;

B is -X-C(R<sup>11</sup>)(R<sup>12</sup>)OR<sup>13</sup>

wherein  $R^{11}$  is hydrogen, alkyl having 1 to 4 carbon atoms;  $R^{13}$  is hydrogen, acyl having 1 to 14 carbon atoms, aroyl having 6 to 15 carbon atoms, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, or t-butyl; X is the following:

1) -CH<sub>2</sub>-CH<sub>2</sub>-,

- 2) -CH=CH-; or
- 3) -C<sub>=</sub>C-; and

R<sup>12</sup> is the following:

1) normal alkyl having 1 to 12 carbon atoms, or branched alkyl having 3 to 14 carbon atoms;

10 2) -Z-Ar<sup>2</sup>

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wherein Z is defined as the same as the above, and  $Ar^2$  represents phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, or phenyl substituted by at least one chlorine; bromine, fluorine, iodine, trifluoromethyl, alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl or phenoxy;

3) -C<sub>t</sub>H<sub>2t</sub>OR <sup>14</sup>

wherein C<sub>t</sub>H<sub>2t</sub> is defined as the same as the above, and R<sup>14</sup> represents normal alkyl having 1 to 6 carbon atoms, branched alkyl having 3 to 6 carbon atoms, phenyl, phenyl substituted by at least one chlorine, bromine, fluorine, iodine, trifluoromethyl, alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl or phenoxy, cyclopentyl, cyclohexyl, or cyclopentyl or cyclohexyl substituted by 1 to 4 normal alkyl groups having 1 to 4 carbon atoms;

14.

4) -Z-R<sup>3</sup> ·

wherein Z and R<sup>3</sup> are defined as the same as the above;

5) -C,H2,-CH=C(R15)R16

wherein  $C_tH_{2t}$  is defined as the same as the above, and  $R^{15}$  and  $R^{16}$  each represent hydrogen, methyl, ethyl, propyl, or butyl, or

6) -C<sub>0</sub>H<sub>20</sub>-C C-R<sup>17</sup>

wherein u is an integer of 1 to 7,  $C_uH_{2u}$  represents normal or branched alkyl, and  $R^{17}$  represents normal alkyl having 1 to 6 carbon atoms (when m = 3, branched ethylene  $C_2H_4$  and methyl as  $R^{17}$  are excluded);

E is hydrogen or -OR 18

wherein  $R^{18}$  represents acyl having 1 to 12 carbon atoms, aroyl having 7 to 15 carbon atoms, or  $R^2$  (wherein  $R^2$  is defined as the same as the above), and

the formula represents the d. I or dI form]

- 11. A cervical ripening method according to Claim 10, wherein A is -(CH<sub>2</sub>)<sub>m</sub>-, -CH=CH-CH<sub>2</sub>-, -CH<sub>2</sub>-CH=CH-, -CH<sub>2</sub>-O-CH<sub>2</sub>-, -CH=CH-, -O-CH<sub>2</sub>-, or -C...C- (m is 1 or 2)
  - 12. A cervical ripening method according to Claim 10, wherein A is -( $CH_2$ )<sub>2</sub>-, -CH=CH-, or -O-CH<sub>2</sub>-.

FIG. 1

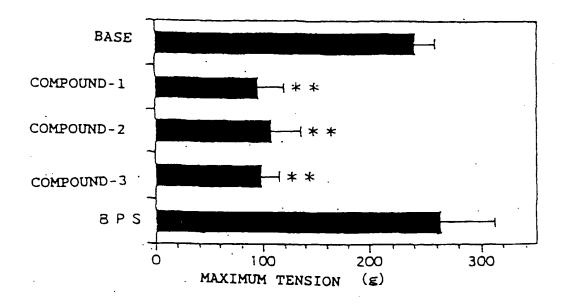
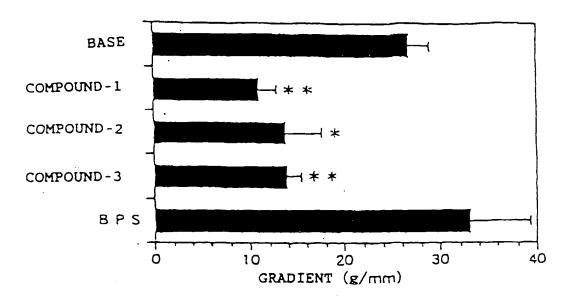


FIG. 2



## INTERNATIONAL SEARCH REPORT

International application No. PCT/JP98/04165

A CLAS	SIFICATION OF SUBJECT MATTER			
Int.Cl <sup>4</sup> A61K31/557, C07D307/93				
According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED				
Minimum of Int	documentation searched (classification system follow . C1 A61K31/557, C07D307/93	ed by classification symbols)		
	ation searched other than minimum documentation to			
Electronic	data base consulted during the international search (n	ame of data base and, where practicable, a	sarch terms used)	
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category	Citation of document, with indication, where a	appropriate, of the relevant passages	Relevant to claim No.	
X	OKAWA T. "BIOSYNTHESIS OF PROSTAGLANDINS AT TERM", Nippon Sanka Fujinka Gakkai Zasshi, Vol. 42, No. 7, pages 732-738, 1990		1-3 4-6	
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X A	Tetsuya Watanabe, "Basic Study on Cervical Maturing — Centering Elastic Modules of Rat Cervical Canal (in Japanese)", Acta Obstetrica et Gynaecologica Japonica, Vol. 40, No. 1, pages 1 to 8, 1988		1-3 4-6	
A	JP, 7-505860, A (Medical Research Council), 29 June, 1995 (29. 06. 95) 4 WO, 93/09796, Al & EP, 543476, Al 4 US, 5624670, A		1 – 6	
Further	r documents are listed in the continuation of Box C.	See patent family soney		
See patent family annex.  Special entegories of cited documents  document defining the general state of the art which is not considered to be of particular relevance entire document their published on or after the international filing date. "T date and not in conflict with the application but cited to understand the principle or theory anderlying the invention date on document which any throw doubts on priority claims of or which is clud to entablish the publication date of another citation or other special reason (as specified)  O' document referring to an oral disclosure, was, exhibition or other masses  P' document published prior to the international finag date but inter them the priority date claimed invention of the international search the priority date claimed in the priority date claimed.  Date of the actual completion of the international search 14 December, 1998 (14. 12. 98)  Date of mailing of the international search 22 December, 1998 (22. 12. 98)				
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